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Secondary Immune Response in a Vaccinated Population during a Large Measles Epidemic

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The rates of secondary immune response (SIR) and secondary vaccine failure (SVF) during a measles epidemic (10,184 notifications) were evaluated. A patient with SIR was defined as a subject for whom all sera were immunoglobulin G (IgG) positive and IgM negative with a significant increase in complement fixation titer. A patient with SVF was defined as a vaccinated symptomatic subject showing a SIR. Sequential sera from 898 subjects were tested for measles antibody by enzyme-linked immunosorbent assay (IgG and IgM) and by complement fixation. Evidence of recent anti-measles virus specific immune response was found in 496 subjects (55.5%). The vaccination rate was estimated at 74.6% (99% confidence interval [CI], 67.9 to 80.7%). The number of exposed vaccinated subjects was estimated at 370 (74.6% of 496). The SIR rate was 4.03% (20 of 496) (99% CI, 2.1 to 6.9%) among subjects with immune response. These 20 subjects were 2 with measles (Centers for Disease Control's definition), 6 with measles with rash of unknown duration, 8 with presumed measles with either rash or fever, 3 asymptomatic subjects (2 with recent contact with a measles case), and 1 undocumented subject. Since 3 patients with SIR were asymptomatic and 2 others were documented as not vaccinated, there was a maximum of 15 probable occurrences of SVF among the 20 patients with SIR. The SVF rate among exposed vaccinated subjects was estimated at 4.05% (15 of 370) (99% CI, 1.9 to 7.5%). In conclusion, neither prior vaccination nor detectable SIR ensures protective immunity. Measles virus may induce asymptomatic SIR in IgG-seropositive subjects. SVF led to typical or modified measles but did not seem to have played an important role during this epidemic.

In a secondary immune response (SIR) following measles virus immunogenic contact, there is an increase in anti-measles virus immunoglobulin G (IgG) antibody (measles-IgG) titer (10, 14), usually without a detectable production of anti-measles virus IgM antibody (measles-IgM) (3, 10). There have been reports indicating that both measles-IgG and measles-IgM might be detected in some patients with SIR (8, 15). However, a restrictive case definition of a SIR which excluded measles-IgM-positive subjects was adopted in most of the published studies (4, 5, 7, 16).

The frequency of SIR during measles outbreaks and its relationship with clinical status are not fully known (5). Measles-IgM-negative patients with SIR were identified among immunized patients with measles (4, 7), modified measles (4, 5), and mild measles (16), suggesting that the capacity for SIR does not always provide protective immunity (16). Also, increases in measles-IgG titers in vaccinated asymptomatic subjects following measles exposure have been reported (6, 11), suggesting that contact with wild measles virus may act as a booster to the immune system in vaccinated subjects without causing any symptoms. These results suggest that different levels of protection against measles exist in immunized subjects. They also suggest that secondary vaccine failure (SVF) might play a role in vaccinated populations during measles outbreaks.

During a measles outbreak in Dane County, Wisc., in 1986, 10 patients with SVF were identified among 182 patients with clinical measles known to have been previously vaccinated (SVF rate, 5.4%) (5). In another measles outbreak in British Columbia, Canada, in 1985 to 1986, 9 patients with measles were diagnosed among 175 subjects with previous serological confirmation of immune status following previous vaccination (SVF rate, 5.1%) (7). These data suggest that SVF has not played an important role during recent measles outbreaks in North America. However, to our knowledge, no large-scale study using a sensitive technique such as an enzyme-linked immunosorbent assay (ELISA) has been carried out to estimate the occurrence of SIR and SVF during a large measles epidemic in North America.

During a measles epidemic in Québec in 1989 (10,184 reported cases [1]), our laboratory received serum samples from 4,195 subjects for measles serology. Acute- and convalescent-phase sera (paired sera) were received for 898 of these 4,195 subjects. Paired sera were tested by using a commercial measles-IgM and measles-IgG ELISA and by complement fixation assay (CF). To our knowledge, it is the first time that so many paired sera within an epidemic have been analyzed for both measles-IgM and measles-IgG by using ELISA and CF. With these data, we were able to verify that the occurrence of SIR and SVF during this large measles epidemic was as low as the one reported previously during smaller outbreaks in a vaccinated population (5, 7).

MATERIALS AND METHODS

Sample. During the 1989 measles epidemic in Québec, 10,184 measles cases were reported (1). A single serum sample (n = 3,297 subjects) or paired serum samples (n = 898 subjects) were received in our laboratory over an 8-month period. Convalescent-phase serum was requested when acute-phase serum was measles-IgM negative or equivocal. The subjects' ages ranged from 4 months to 63 years (mean, 13 years). Females and males were equally represented. Based on a sample of 1,235 subjects, the

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distribution of subjects for whom measles serology was requested was as follows: 67% patients with clinical measles according to the Centers for Disease Control (CDC) definition (2), 21% patients with clinical measles with rash of unknown duration, 9% patients with presumed measles with either rash or fever, and 3% asymptomatic subjects (9).

The 898 paired serum samples received for measles serology were studied for the evaluation of the occurrence of SIR during the epidemic. The first serum sample was taken on average 4.9 days after the onset of symptoms (median, 4; mode, 4; range, 0 to 56; 95th percentile, 10 days). The second serum sample was taken on average 18.5 days after the onset of symptoms (median, 18; mode, 20; range, 1 to 51; 95th percentile, 25 days). The time lapse between paired sera was on average 15.4 days (median, 14; mode, 14; range, 1 to 42; 95th percentile, 22 days). Most specimens were analyzed for the presence of measles-IgM within 24 h of reception and then frozen until measles-IgG detection and CF tests could be carried out on paired sera.

Serological tests. Enzygnost Measles ELISA kit (Behring, Behringwerke AG, Marburg, Germany) was used to detect measles-IgM or measles-IgG with the appropriate conjugate. Since excess of IgG or the presence of rheumatoid factor may interfere in IgM solid-phase enzyme immunoassay (13), measles-IgM ELISA was carried out with sera diluted in RF Absorbent (sheep anti-human IgG; Behring) to precipitate IgG immunoglobulins and IgG-linked rheumatoid factor if present. ELISA was performed following manufacturer's instructions. Optical densities were interpreted following a validated in-house algorithm (9).

The Laboratory Branch CF micromethod (17) was carried out to detect complement-fixing antibody (CF-Ab). Paired sera were analyzed within the same run. Each run included low positive, high positive, and negative controls as previously described (9). A significant increase in CF-Ab titer (CF/up) was defined as a fourfold increase between acute- and convalescent-phase serum CF-Ab titers (14).

Definitions. According to the CDC's case definition of clinical measles (2), a patient with measles is a subject showing a fever of ≥38.3°C (if measured) with a generalized rash lasting at least 3 days and cough, coryza, or conjunctivitis.

A restrictive case definition of a SIR, which excluded measles-IgM-positive subjects, was adopted so that only true SIR would be studied. A SIR was defined as the presence of measles-IgG in both acute- and convalescent-phase sera as detected by ELISA, without detectable measles-IgM in either serum and with a CF/up. Moreover, the acute-phase serum had to be taken within 10 days of the onset of symptoms; the convalescent-phase serum had to be taken at least 5 days but no more than 30 days after the acute-phase serum.

A patient with SVF was a vaccinated subject who became symptomatic and developed a SIR.

Data collection and analysis. Demographic and laboratory data were downloaded from our main laboratory data management system (EPIC; EPIC SYSTEMS Corp., Madison, Wisc.) to a dBase data file using dBase IV software (Ashton Tate, Torrance, Calif.) running on a Turbo IBM-PC XT-compatible computer. Clinical and immunization data were obtained from regional health authorities or attending physicians. Computerized demographic, clinical, and immunization information was validated by the attending physician or by comparison with information from other registers. All computerized laboratory data were validated by using laboratory files.

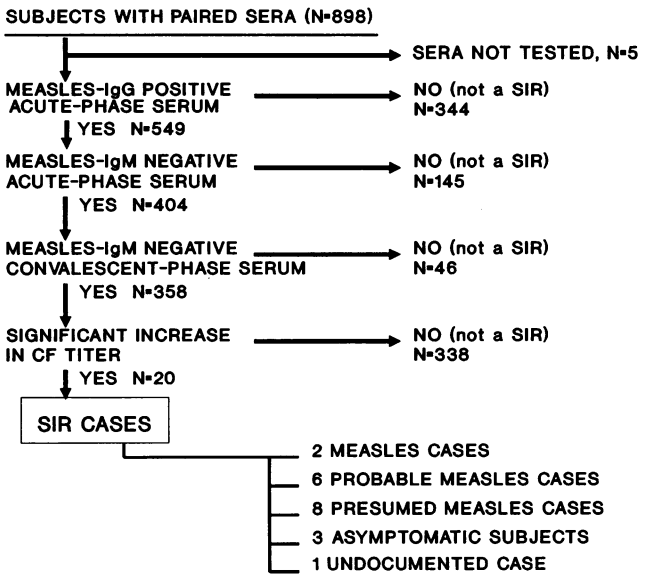

FIG. 1. Dichotomous classification of the 898 subjects with paired sera leading to identification of the 20 patients with SIR.

To compute the time lapse between onset of symptoms and phlebotomy, the date of the first reported symptom was used instead of the date of onset of the rash, which was not available for 66% of the documented cases.

RESULTS

Serological results. Evidence of recent measles virus immunogenic contact was found in 496 of 893 subjects (55.5%); serum samples from 5 of 898 subjects were not tested. Measles-IgM was detected in acute-phase serum samples from 266 subjects. Measles-IgM was detected in convalescent-phase serum samples from 147 subjects showing acute-phase measles-IgM negative serum and from 47 subjects with acute-phase measles-IgM equivocal serum. Thirty subjects with measles-IgG-positive acute- and convalescent-phase sera never became measles-IgM positive (20 measles-IgM-negative and 10 measles-IgM-equivocal subjects) but showed a CF/up. Three measles-IgM-seronegative subjects showed a measles-IgG seroconversion without CF/up. Three subjects showed measles-IgG seroconversion and CF/up without measles-IgM seropositivity.

Number of subjects showing a SIR. Among the 898 subjects for whom paired sera were received, 20 subjects showed a SIR as defined here (Fig. 1). Thus, the SIR rate among subjects showing evidence of recent measles virus immunogenic contact was 20 of 496 (4.03%; 99% confidence interval, 2.1 to 6.9%). Delays in taking the serum sample and the CF-Ab titer evolution for these 20 subjects are given in Table 1.

Time between taking of paired sera and CF/up. The relationship between the number of days between taking of paired sera and CF/up was studied to evaluate the risk of CF/up nondetection due to a convalescent serum taken too early, thereby leading to underestimation of SIR. Study of 209 subjects with documented symptoms showed that the average time between paired sera was 15.3 days (median, 15 days; mode, 14 days; range, 2 to 32 days) for subjects who showed a CF/up (n = 143) and 12.3 days (median, 14 days; mode, 14 days; range, 1 to 96 days) for subjects who showed

TABLE 1. CF titers of sera from subjects showing SIR[a]

Subject no.	Delay		CF titer	
	1st[b]	2nd[c]	1st	2nd
1	3	18	<8	32
2	0	15[d]	<8	32
3	0	28[d]	<8	32
4	8	23	<8	64
5	5	20	<8	64
6	0	22[d]	<8	512
7	3	20	<8	512
8	2	15	8	1,024
9	0	24[d]	8	1,024
10	0	19[d]	16	512
11	3	20	32	512
12	2	16	32	1,024
13	7	23	64	512
14	4	25	64	512
15	2	28	64	1,024
16	0	13[d]	128	512
17	1	15	128	1,024
18	2	15	128	1,024
19	−1	13	128	1,024
20	0	13[d]	128	1,024

[a] All sera were measles-IgM negative and measles-IgG positive as detected by ELISA.
[b] Delay between the onset of symptoms and the taking of the first serum sample. Day 0 indicates that the onset of symptoms was not documented or that the subject was asymptomatic.
[c] Delay between the onset of symptoms and the taking of the second serum sample.
[d] Delay between the taking of the first and second serum samples when the onset of symptoms was undocumented or occurred in asymptomatic subjects.

TABLE 2. Clinical and immunization data for subjects showing SIR

Subject no.	Age (yr)	Vaccination (age in mo)[a]	Clinical data[b]						Note(s)[c]
			KPK	FVR	RSH	CGH	CRZ	CNJ	
1	44	— (—)	—	Yes	Yes	Yes	—	—	g
2	22	— (—)	No	No	No	No	No	No	a
3	16	— (—)	No	No	No	No	No	No	
4	21	No (—)	—	Yes	Yes	Yes	—	—	g
5	11	Yes (16)	—	Yes	Yes	Yes	—	Yes	b, f
6	24	No (—)	No	No	No	No	No	No	a, c
7	17	Yes (—)	Yes	Yes	Yes	Yes	Yes	No	b, f, h
8	12	Yes (12)	No	Yes	Yes	—	—	—	b, f
9	13	No (—)	—	Yes	Yes	No	No	No	d, g
10	20	Yes (—)	—	Yes	—	Yes	—	—	f
11	15	— (—)	—	—	Yes	Yes	—	Yes	b
12	14	Yes (8)	—	Yes	Yes	Yes	Yes	Yes	g
13	17	Yes (151)	No	Yes	Yes	No	Yes	Yes	f, h
14	19	Yes (—)	No	Yes	Yes	Yes	Yes	Yes	g
15	7	Yes (12)	No	Yes	Yes	Yes	Yes	No	f
16	14	— (—)	—	—	—	—	—	—	
17	12	— (—)	Yes	No	Yes	No	No	No	
18	12	Yes (12)	Yes	Yes	Yes	No	No	No	g, h
19	9	— (—)	—	Yes	Yes	—	—	—	e, f
20	16	Yes (14)	No	No	Yes	—	No	No	

[a] —, no information available.
[b] KPK, Koplik spots; FVR, fever; RSH, rash; CGH, cough; CRZ, coryza; CNJ, conjunctivitis; —, no information available.
[c] a, asymptomatic subject with a contact within the previous week with a patient with documented measles; b, photophobia; c, subject who had had measles when younger; d, emergency ward patient; e, nondiagnostic rash; f, documented fever of ≥38.3°C.; g, reported fever of unspecified degree; h, rash for ≥3 days.

a stable CF-Ab titer or remained nonreactive (n = 66). There was no significant difference in the distribution of time lapses between paired sera for these two groups of subjects (Wald-Wolfowitz test; $P > 0.9$).

Clinical and immunization data for subjects showing a SIR. All clinical and immunization data for subjects showing a SIR (Table 2) were validated with the attending physicians. Two subjects (no. 7 and 13) met the CDC definition of a measles case; both of them were known to have been vaccinated. Six subjects (no. 1, 4, 5, 12, 14, and 15) met the CDC description of clinical measles but with a rash of unknown duration; four of these six subjects were known to have been vaccinated. Eight subjects (no. 8, 9, 10, 11, 17, 18, 19, and 20) were symptomatic but presented an incomplete CDC clinical measles picture; four of these eight subjects were known to have been vaccinated. Three subjects (no. 2, 3, and 6) remained asymptomatic; two of them had a known contact within the previous week with a patient with documented measles. One asymptomatic subject was said to have had measles in the past. Medical records were not available for one subject (no. 16).

Estimation of the rate of SVF. Among the 20 SIR subjects, 3 subjects were asymptomatic (no. 2, 3, and 6) and 2 other subjects were documented as not vaccinated (no. 4 and 9), thus leaving a maximum of 15 symptomatic vaccinated subjects with probable SVF. Of the 898 in the paired-serum group, 578 subjects had an unknown vaccination status and 320 were documented as either vaccinated (n = 239) or not vaccinated (n = 81), giving an estimated vaccination rate of 74.6% (239 of 320) (99% confidence interval, 67.9 to 80.7%). On the basis of this percentage, the number of vaccinated subjects among subjects showing evidence of recent measles virus immunogenic contact (n = 496) was estimated at 370 subjects. On the basis of these assumptions, the rate of SVF in vaccinated subjects showing evidence of recent measles virus immunogenic contact was estimated at 4.05% (15 of 370) (99% confidence interval, 1.9 to 7.5%).

DISCUSSION

The rate of SIR was estimated at 4.03% in a sample of 898 subjects of whom 496 showed evidence of a recent measles virus immunogenic contact. This estimation could be a misestimation of the actual rate if either the number of identified patients with SIR was inaccurate or if the 496 subjects were not representative of the infected cases.

Accurate identification of SIR depends mostly on the sensitivity and specificity of the three techniques used and on the proper timing of the specimen collection.

An overestimation of SIR could have occurred if the ELISA kit was not sensitive enough to detect low titers of measles-IgM. The measles-IgM detection sensitivity for CF-confirmed measles cases was high: 96.6 and 100% for vaccinated and nonvaccinated subjects, respectively, when the Enzygnost kit was used (9). Also, interfering IgG, which might have caused false-negative results because of competition for attachment sites in the ELISA well, were eliminated when the IgM ELISA was performed. Thus, 40 (20 paired sera) false-negative measles-IgM ELISA results caused by an insensitive assay or interfering IgG are unlikely.

The number of patients with SIR could have been overestimated if some subjects had had an IgM immune response but both serum samples had been taken either too early or too late to detect measles-IgM. In our laboratory, the daily rate of detected IgM seropositivity for subjects who became

IgM positive within 30 days increased from 40 to 90% for sera taken 1 to 7 days post onset of symptoms and up to 100% for sera taken 16 to 30 days post onset (9). Of the 20 SIR cases identified, nine convalescent-phase serum samples were taken between 16 and 30 days post onset of symptoms, four convalescent-phase serum samples were taken between 13 and 15 days post onset, and four others were taken 19, 22, 23, and 28 days after the first serum. It is unlikely that measles-IgM, if induced, would have been missed in these 17 late serum samples, since there was a 90% probability (9) of detecting measles-IgM if ever induced in these sera. Based on our experience and on reported Measles Enzygnost IgM detection rate in relationship to phlebotomy timing (12), it is unlikely that the 40 measles-IgM-negative serum samples were false negatives due to inappropriate serum collection timing.

An underestimation of SIR would have occurred if the time between paired sera for subjects who did not show a CF/up was too short to allow CF seroevolution to occur. The time between paired sera was on average 3 days longer for subjects who showed a CF/up (15.3 days) than for those who did not (12.3 days). However, this difference does not represent a statistically significant difference in the distribution of time lapses between paired sera for these two groups (Wald-Wolfowitz test; $P > 0.9$). The Wald-Wolfowitz test permits us to detect significant differences in medians, dispersion, and skewness between two distributions.

A large number of IgM false-positive results would have led to an underestimation of the SIR rate, since measles-IgM-positive subjects were excluded from the SIR subject group. However, measles-IgM-positive results were strongly associated with IgG seroconversion, CF/up, and clinical measles cases (9). Also, serum treatment with RF Absorbent eliminated potential IgM false-positive results due to the rheumatoid factor. Both facts indicate that a large number of IgM false-positive results leading to an underestimation of SIR rate is highly unlikely.

Since a weak measles-IgM response in patients with SIR has been reported (8, 15), the percentage observed (4.03%) may underestimate the true occurrence of SIR during the epidemic because of the restrictive definition of SIR used, which included only measles-IgM-negative subjects. However, the addition of the 10 subjects who were measles-IgG positive and measles-IgM equivocal with a CF/up would have increased the SIR rate only to 6.04% (30 of 496). Thus, it is unlikely that the restrictive definition of SIR used led to gross underestimation of SIR due to the exclusion of subjects showing measles-IgM-equivocal serum.

Because the study group included only subjects for whom paired sera were received, there was the possibility of a biased estimate of the occurrence of SIR due to overrepresentation of subjects with acute-phase measles-IgM-negative serum, since a convalescent-phase serum was more likely to be taken for those subjects. A higher proportion of measles-IgM-negative acute-phase sera were received from the subjects from whom paired sera were obtained (564 of 898; 62.8%) than from the single-serum subjects (1,857 of 3,297; 57%) (chi-square test; $P = 0.00056$). Thus, a slight overestimation of the SIR rate due to oversampling of acute-phase measles-IgM-negative sera may have occurred.

Our results allowed us to estimate the rate of SVF during this epidemic to be 4.05%. Rates of SVF of 5.4% among vaccinated patients with clinical measles (5) and 5.1% among vaccinated subjects (7) have been reported during measles outbreaks. These rates, within the same order of magnitude as the one we estimated, suggest that SVF does not play an important role during measles outbreaks in vaccinated populations in North America.

In this study, three asymptomatic subjects showed a SIR; two of three had had a known contact within the previous week with a patient with documented measles. Since these two subjects were initially measles-IgG positive, remained measles-IgM negative, and showed an immune response without symptoms, we think that they were protected against measles and that the contact with the wild measles virus may have acted as a booster to the immune system, inducing an asymptomatic SIR.

In conclusion, our data indicate that a history of prior vaccination or the capacity for a SIR is not always associated with protective immunity and that in fact SIR may be associated with typical or modified measles. Our data confirm that, for some subjects showing serological evidence of previous measles antigen immune stimulation, the contact with wild measles virus may act as a booster to the immune system, inducing an asymptomatic SIR. Although our results may have led to a slight misestimation of the number of SIR cases, they indicate that SVF leading to typical or modified measles did not occur frequently during the 1989 measles epidemic in Québec and probably did not play an important role during that epidemic. This assumption is also supported by the fact that 96.6% of the tested sera from documented vaccinated measles cases were IgM positive (9), suggesting that primary vaccine failure was predominant.

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